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10/736,301	12/15/2003	Michael Graham Cordingley	9/270A	5463

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EXAMINER	
ISSAC, ROY P	
ART UNIT	**PAPER NUMBER**
1623	

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/736,301	CORDINGLEY, MICHAEL GRAHAM	
	Examiner	Art Unit	
	Roy P. Issac	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/29/04; 3/15/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

This application claims priority under 35 U.S.C § 119(e) from provisional application 60/433,690 filed 12/16/2002. Claims 1-15 are currently pending in the application and are examined on the merits herein.

Claim Objections

Claim 3 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 3 does not further limit the independent claim1 from which it depends.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the particular and specific inhibitors of CYP450 in the combination with the compound of formula I herein used in a method for treating HIV-1 infection, does not reasonably provide

enablement for any substances or compounds represented by "inhibitors of CYP450" recited in the claims herein.

The recitation, "inhibitors of CYP450", is seen to be merely functional language.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to the treatment of HIV infection.

The relative skill of those in the art: The relative skill of those in the art is high.

The breadth of the claims: The instant claims are deemed very broad since these claims may reasonably encompass not only those known but also unknown

"inhibitors of CYP 450" as of the instant filing date, and even those future known "inhibitors of CYP 450".

The amount of direction or guidance presented:

Functional language at the point of novelty, as herein employed by Applicants, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997) at 1406: stating this usage does "little more than outline goal appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate". The CAFC further clearly states that "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405(emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus.." at 1406 (emphases added).

However, the specification fails to clearly define which compounds are inhibitors of cytochrome P450 or CYP3A4. The specification states, "As used herein the terms "inhibitor of the cytochromes P450" or "inhibitor of CYP3A4" or "CYP 450 inhibitor" refer to any member of the class of pharmaceuticals and/or natural products which inhibit at least the CYP3A4 isoform of the cytochromes P450." (Page 5, Paragraph 2, lines 6-14). The specification further notes that

the class is not limited to the listed pharmaceuticals. (Page 5, Paragraph 2, lines 7-15). In order for one of ordinary skill in the art to determine which of the cytochromes P450 inhibitors other than the ones specified will be useful in combination with the compound of formula I, undue experimentation is necessary.

Thus, Applicants functional language at the points of novelty fails to meet the requirements set forth under 35 U.S.C. 112, first paragraph. Claims employing functional language at the exact point of novelty, such as Applicants', neither provide those elements required to practice the inventions, nor "inform the public during the life of the patent of the limit of monopoly asserted" (*General Electric Company v. Wabash Appliance Corporation et al.* 37 USPQ at 468 (US Supreme Court 1938)).

The predictability or unpredictability: the instant claimed invention is highly *unpredictable* as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully described genus, visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, as discussed above in *University of California v. Eli Lilly and Co.* Hence, in the absence of fully recognizing the

identity of the members genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having claimed functional properties in the pharmaceutical compositions herein.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutic effects, side effects, and especially serious toxicity that may be generated by drug-drug interactions when and/or after administering to a host (e.g., a human)

Combination therapy, and drug-drug interactions are known in the art to have various effects, and when physicians use several drugs in combination, they face the problem of knowing whether a specific combination in a given patient has the potential to result in an interaction, and if so, how to take advantage of the interaction if it leads to improvement in therapy or how to avoid the consequences on an interaction if they are adverse. A potential drug interaction refers to the possibility that one drug may alter the intensity of the pharmacological effects of another drug if given concurrently. The net result may be enhanced or diminished effects of one or both of the drugs, or the appearance of new effects, which is not seen with either drug alone. The frequency of significant beneficial or adverse effects is unknown. The interaction between the drugs may be pharmacokinetic, i.e. alteration of the absorption, distribution, or elimination of one drug by another, or may be pharmadynamic, i.e. interactions between agonists and antagonists at drug receptors. The most important drug-drug interactions occur with drugs that have serious toxicity and low therapeutic

index, such that relatively small changes in drug level can have significant adverse consequences. Additionally, drug-drug interactions can be clinically important if the disease being controlled with the drug is serious or potentially fatal if left under treated. Drugs are known to interact at any point during their absorption, distribution, metabolism, or excretion; the result being an increase or decrease in concentration of the drug at the site of action. As individuals vary in their rates of disposition of an given drug, the magnitude of an interaction that alters pharmacokinetic parameters is not always predictable, but can be very significant. See Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 10th Edition, McGraw-Hill Medical Publishing Division, 2001, pages 54-56. **Thus, the teachings of the book clearly support that the instant claimed invention, administering a** combination of any "one or more inhibitors of CYP 450" and the compound of formula I to a human **is highly unpredictable.**

The presence or absence of working examples and the quantity of experimentation necessary:

Only one compound, ritonavir in combination with the compound of formula I is disclosed in an example in the specification. Moreover, it is noted that the specification fails to provide working examples, i.e., testing results or data to demonstrate the instant compositions (different combinations of the claimed compounds) to be administered to a host, i.e., a human, in treating for HIV for any compounds other than ritonavir. Thus, the evidence in the examples is also

not commensurate in scope with the claimed invention and does not demonstrate criticality of a claimed range of the ingredients in the claimed composition.

Note that the court of *In re Curtis* held that "a patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when... the evidence indicates ordinary artisans could not predict the operability .....of any other species." (emphasis added, see *In re Curtis* 354 F.3d 1347, 69 USPQ2d 1274, Fed. Cir. 2004). In the instant application, the combination of ritonavir, a pharmaceutical well known for its ability to accentuate the activity of other HIV drugs, in combination with the compound of formula I does not predict operability of other "inhibitors of CYP 450" with said compound.

Thus, the specification fails to provide clear and convincing evidence in sufficient support of the broad use of any compounds having those functions recited in the instant claims. As a result, necessitating one of skill to perform an exhaustive search and undue experimentation for the embodiments of any known and unknown compounds having those functions encompassed in the instant claims suitable to practice the claimed invention.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors, the case *University of California v. Eli Lilly and Co.* (CAFC, 1997) and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in *undue experimentation* to test all compounds encompassed in the instant claims and their combinations employed in the claimed compositions to be administered to a host, with no assurance of success.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The expression "a human in need of such treatment" in claim 6 renders the claim indefinite. The expression does not show which diseases, disorders or symptoms are treated by the use of the combination.

Claims 1-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation "administering ...." but missing "to said human" in the claims renders these claims indefinite. Thus, the method is unclear as to administering to whom for the treatment herein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simoneau B et. al (U.S. Patent No. 6,420,359; PTO-1449, Included by the applicant) in view of Malaty et. al.(PTO-1449, Included by the applicant)

The '359 patent is drawn to the use of the compound of formula I for the treatment of HIV infection. (Claims 1-3, 5 and 8-9; Columns 41-44). The '359 application further discloses the compound of formula I as a non-nucleoside reverse transcriptase inhibitor (NNRTI). (Column 2, lines 30-35). The '359 patent further discloses the use of compound of formula I in the range of 0.1mg - 800 mg per day for a patient weighing 70 kg. (Column 4, last paragraph to Column 1, first paragraph).

The '359 patent does not expressly disclose the co-administration of ritonavir with the compound of formula I, or the use of ritonavir in the claimed dosage range to achieve a reduction in the rate of metabolism of the compound of formula I.

Malaty et. al. teaches that ritonavir is a potent inhibitor of Cytochrome 450 enzyme (CYP 450) and its isozymes, including CYP3A4. (Page 148, Colum1, last paragraph and Column 2, first paragraph). Malaty teaches that ritonavir

slowed the rate of metabolism of two non nucleoside reverse transcriptase inhibitors, delaviridine and efavirenz. (Page 154, Column 2, Section titled Reverse Transcriptase Inhibitors). The rate of availability of the drug measured by AUC measurement showed a 21% increase for Efavirenz in combination with ritonavir. (Page 154, Column 2, Section titled Reverse Transcriptase Inhibitors). Malaty teaches that ritonavir reduces the metabolism, and thus increases the plasma concentration of at least 10 other HIV drugs. (Page 165, Table VII). In case of indinavir, the rate of plasma conecentration, measure by AUC, was increased by 475%. (Page 164, Column 1, Paragraph 2, lines 5-10). Malaty et. al. further teaches dosage regimens of ritonavir in 300 mg, 400 mg 500 mg and 600 mg dosage units. (Page 150, Column 2, last paragraph to Page 151, Column 1, first paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to co-administer ritonavir with the compound of formula I to reduce its rate of metabolism, because ritonavir was well known for its inhibition of the CYP 450 enzyme and its effectiveness in increasing the plasma concentration of HIV drugs.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine ritonavir with the Compound of formula I to slow its metabolism because ritonavir is a potent inhibitor cytochrome 450 enzyme and ritonavir is well known to slow the metabolism of inhibitors of HIV infection.

One of ordinary skill in the art at the time the invention was made would have been motivated to co-administer ritonavir with the Compound of formula I to

slow down the metabolism of said compound because ritonavir is a potent inhibitor cytochrome 450 enzyme and ritonavir is well known to slow the metabolism of inhibitors of HIV infection. The claimed ranges of ritonavir (about 30 mg to 1000 mg) and the compound of formula I (50 –6750 mg) overlaps with the dosages disclosed in the '359 patent for said compound (0.1-800mg) and that disclosed in Malaty et. al for ritonavir (300-600 mg). If the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exits. See *In re Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir 1990). See MPEP § 2144.05 [4-1].

Therefore one of ordinary skill in the art would have reasonably expected that combining a ritonavir with the compound of formula I, both known useful for treating HIV infection, would improve the therapeutic effects for treating the same disease, and/or would produce additive therapeutic effects in treating the same.

It has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simoneau B, (PTO-1449, Included by the applicant) in view of Malaty et. al. (PTO-1449; Included by the applicant).

Simoneau B. discloses the use of the compound of formula I as an inhibitor of HIV-1 reverse transcriptase and as useful for the treatment of AIDS. (Page 7, Paragraph 2, lines 7-13). Simoneau patent further discloses the use of compound of formula I in the range of 0.1mg -800 mg per day for a patient weighing 70 kg. (Page 7, Paragraph 3, lines 19-25).

Simoneau does not expressly disclose the co-administration of ritonavir with the compound of formula I, or the use of ritonavir in the claimed dosage range to achieve a reduction in the rate of metabolism of the compound of formula I.

The disclosure of Malaty et. al. is dicussed above.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine ritonavir with the Compound of formula I to slow its metabolism because ritonavir is a potent inhibitor cytochrome 450 enzyme and ritonavir is well known to slow the metabolism of inhibitors of HIV infection.

One of ordinary skill in the art at the time the invention was made would have been motivated to co-administer ritonavir with the Compound of formula I to slow down the metabolism of said compound because ritonavir is a potent inhibitor cytochrome 450 enzyme and ritonavir is well known to slow the metabolism of inhibitors of HIV infection. The claimed ranges of ritonavir (about 30 mg to 1000 mg) and the compound of formula I (50 –6750 mg) overlaps with

the dosages disclosed by Simoneau for said compound (0.1-800mg) and that disclosed in Malaty et. al for ritonavir (300-600 mg). If the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exits. See *In re Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir 1990). See MPEP § 2144.05 [4-1].

Therefore one of ordinary skill in the art would have reasonably expected that combining a ritonavir with the compound of formula I, both known useful for treating HIV infection, would improve the therapeutic effects for treating the same disease, and/or would produce additive therapeutic effects in treating the same.

It has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

In view of the rejections set forth above, NO claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Roy P. Issac whose telephone number is 571-272-2674. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

8/2/06

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April 28, 2006

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